NOVEL SULFENAMIDE OXIDES

Technical Field

The present invention relates to novel sulfenamide oxides that have physiological activity, particularly an antimicrobial action, methods for their synthesis, pharmaceutical compositions containing them and method of treatment of patients, in particular, those suffering a microbial infection.

Background Art

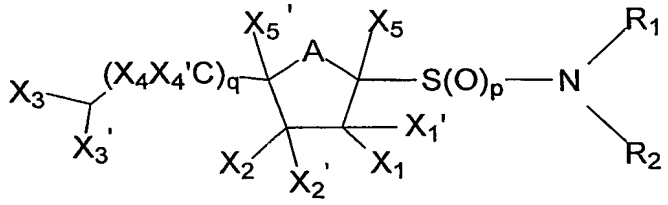
Many bacterial diseases once thought to be on the decline are beginning to re-emerge and annually devastate populations in many countries. This problem is amplified by the emergence of many new drug resistant strains of the microorganisms that cause these diseases. Our interest in the development of carbohydrate-based antimicrobial agents (see, for example, von Itzstein, Wu, *et al.*, 1993; Kok, Campbell, Mackey, & von Itzstein, 1996; Fazli, Bradley *et al.*, 2001) and in glycofuranose chemistry (Owen & von Itzstein, 2000) has led to the discovery of a new class of antimicrobial agents described below. Although significant chemistry and biology has been published (see, for example, Marino, Marino, Miletti, Alves, Colli, & de Lederkremer, 1998; Miletti, Marino, Marino, de Lederkremer, Colli & Alves, 1999; Zhang & Liu, 2001; Brimacombe, Gent & Stacey, 1968; Brimacombe, Da'aboul & Tucker, 1971; Lemieux & Stick, 1975; de Lederkremer, Cirelli & Sznaidman, 1986; Shin & Perlin, 1979; de Lederkremer, Cicero & Varela, 1990; de Lederkremer, Marino & Marino, 2002; Pathak, Pathak, Suling, Gurcha, Morehouse, Besra, Maddry & Reynolds, 2002; Ernst, Hart & Sinay, 2000) in the area of glycofuranose chemistry and biology none to date has provided compounds that are clinically useful antimicrobial medicines. Carbohydrate mimics based on isosteres of the ring structure are well known in the literature and often present interesting biological activities (see, for example, Chapleur, 1998; Lillelund,

Jensen, Liang, & Bols, 2002; Kok, Campbell, Mackey, & von Itzstein, 1996).

Disclosure of the Invention

The present invention is concerned generally with novel sulfenamide oxides that have physiologic activity, in particular, an antimicrobial action.

In a first aspect of the present invention there is provided a compound of general formula (I):



wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted alkenyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted acyl and a carbohydrate moiety;

or R_1 and R_2 together with the nitrogen atom from which they depend form a saturated or unsaturated, optionally substituted heterocyclic group which may include additional heteroatoms selected from the group consisting of O, N and S;

A is selected from the group consisting of O, S, SO, SO_2, Se, Te, NR_8, $CR_9R'_9$, N->O and C(O);

X_1 is selected from the group consisting of OR_3, SR_3, $NR_3R'_3$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_3$, $-N(C=(Z)(T)_nR_3)_2$, N_3, CN, OCN, SCN, OSO_3R_3, OSO_2R_3, $OPO_3R_3R'_3$, $OPO_2R_3R'_3$, $S(O)R_3$, $S(O)_2R_3$, $S(O)_2OR_3$, $PO_3R_3R'_3$, $NR_3NR'_3R''_3$, $SNR_3R'_3$, $NR_3SR'_3$, SSR_3 and R_3, or is an oxo group, =S, $=NOR_3$ or $=CR_3R'_3$ and X_1' is absent, or X_1 is C=(Z) and R_2 is bonded thereto so as to form a cyclic moiety $-C=(Z)NR_1S(O)_p-$;

X_2 is selected from the group consisting of OR_4, SR_4, $NR_4R'_4$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_4$, $-N(C=(Z)(T)_nR_4)_2$, N_3, CN, OCN, SCN, OSO_3R_4, OSO_2R_4, $OPO_3R_4R'_4$, $OPO_2R_4R'_4$, $S(O)R_4$, $S(O)_2R_4$, $S(O)_2OR_4$, $PO_3R_4R'_4$, $NR_4NR'_4R''_4$, $SNR_4R'_4$, $NR_4SR'_4$, SSR_4 and R_4, or is an oxo group, =S, $=NOR_4$ or $=CR_4R'_4$ and X_2' is absent;

X_3 and $X_3'$are independently selected from the group consisting of OR_5, SR_5, $NR_5R'_5$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_5$, $-N(C=(Z)(T)_nR_5)_2$, N_3, CN, OCN, SCN, OSO_3R_5, OSO_2R_5, $OPO_3R_5R'_5$, $OPO_2R_5R'_5$, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2OR_5$, $PO_3R_5R'_5$, $NR_5NR'_5R''_5$, $SNR_5R'_5$, $NR_5SR'_5$, SSR_5 and R_5, or X_3 is an oxo group, =S, $=NOR_5$ or $=CR_5R'_5$ and X_3' is absent;

X_4 is selected from the group consisting of OR_6, SR_6, $NR_6R'_6$, hydrogen, halogen, $-(Y)_mC=(Z)(T)_nR_6$, $-N(C=(Z)(T)_nR_6)_2$, N_3, CN, OCN, SCN, OSO_3R_6, OSO_2R_6, $OPO_3R_6R'_6$, $OPO_2R_6R'_6$, $S(O)R_6$, $S(O)_2R_6$, $S(O)_2OR_6$, $PO_3R_6R'_6$, $NR_6NR'_6R''_6$, $SNR_6R'_6$, $NR_6SR'_6$, SSR_6 and R_6, or is an oxo group, =S, $=NOR_6$ or $=CR_6R'_6$ and X_4' is absent;

X_5 is selected from the group consisting of hydrogen, CN, $-C=(Z)(T)_nR_{11}$, $S(O)R_{11}$, $S(O)_2R_{11}$, $S(O)_2OR_{11}$, $PO_3R_{11}R'_{11}$, optionally substituted alkyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl;

X_1', X_2', X_4' and X_5' are the same or different and are selected from the group consisting of hydrogen, CN, optionally substituted alkyl, optionally substituted alkaryl, optionally substituted aryl, optionally substituted aralkyl, and optionally substituted acyl;

or one of X_1 and X_2, X_2 and X_5', X_5' and A when A

contains a carbon or nitrogen atom, X_5 and A when A contains a carbon or nitrogen atom, and X_5 and X_1 together constitute a double bond, or X_5' and X_4 or X_3 and X_4 together constitute a double bond, or R_1 and X_1, R_2 and X_1, R_1 and X_2, R_2 and X_2, R_1 and X_5, R_2 and X_5, R_1 and X_5', R_2 and X_5', X_1 and X_2, X_2 and X_3, X_2 and X_4, X_3 and X_4, X_1 and X_1', X_2 and X_2', X_3 and X_3' or X_4 and X_4' together form part of a ring structure which optionally includes at least one heteroatom selected from O, S and N and is optionally substituted;

m and n are independently zero or one and Y, Z and T are independently selected from the group consisting of O, S, and NR_{10}

p is 1 or 2

q is 0 or 1;

R_3, R'_3, R''_3, R_4, R'_4, R''_4, R_5, R'_5, R''_5, R_6, R'_6, R''_6, R_7, R_8, R_9, R'_9, R_{10}, R_{11} and R'_{11} are the same or different and are selected from the group consisting of hydrogen, optionally substituted alkyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted alkenyl which may be interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted aryl, optionally substituted heterocyclic, optionally substituted aralkyl which may be interrupted within the alkyl moiety by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7 and $-(Y)_mC=(Z)(T)_n-$, optionally substituted acyl and a carbohydrate moiety;

with the proviso that at least two of X_1, X_2, X_3 and X_4 are other than hydrogen or a group linked to the ring through a carbon-carbon bond;

or a pharmaceutically acceptable salt thereof.

It will be appreciated that the manner of representing substituents in the foregoing general formula does not imply any particular stereochemistry or

orientation for the substituents.

The term "alkyl" used either alone or in a compound word such as "optionally substituted alkyl" or "optionally substituted cycloalkyl" denotes straight chain, branched or mono- or poly- cyclic alkyl. Examples of straight chain and branched C alkyl include methyl. ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl and the like.

The term "alkenyl" used either alone or in compound words such as "alkenyloxy" denotes groups formed from straight chain, branched or cyclic alkenes including ethylenically mono-, di- or poly-unsaturated alkyl or

cycloalkyl groups as defined above. Examples of C_{4-30} alkenyl include butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1-4,pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

The term "acyl" used either alone or in compound words such as "optionally substituted acyl" or "optionally substituted acyloxy" denotes an aliphatic acyl group or an acyl group containing an aromatic ring, which is referred to as aromatic acyl, or a heterocyclic ring, which is referred to as heterocyclic acyl, preferably C_{1-30} acyl. Examples of acyl include straight chain or branched alkanoyl such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; cycloalkylcarbonyl such as cyclopropylcarbonyl cyclobutylcarbonyl, cyclopentylcarbonyl and cyclohexylcarbonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthylpropanoyl and naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacrylyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); heterocycliccarbonyl; heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and

tetrazolylacetyl; and heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl and heterocyclichexenoyl.

The term "aryl" used either alone or in compound words such as "optionally substituted aryl", "optionally substituted aryloxy" or "optionally substituted heteroaryl" denotes single, polynuclear, conjugated and fused residues of aromatic hydrocarbons ("carbocyclic aryl" or "carboaryl") or aromatic heterocyclic ("heteroaryl") ring systems. Examples of carbocyclic aryl include phenyl, biphenyl, terphenyl, quaterphenyl, phenoxyphenyl, naphtyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl, azulenyl, chrysenyl. Examples of heteroaryl include pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrryl, pyrrolyl, furanyl, imadazolyl, pyrrolydinyl, pyridinyl, piperidinyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. Preferably, a carbocyclic aromatic ring system contains 6-10 carbon atoms and an aromatic heterocyclic ring system contains 1 to 4 heteratoms independently selected from N, O and S and up to 9 carbon atoms in the ring.

The term "heterocyclyl" or equivalent terms such as "heterocyclic" used either alone or in compound words such as "optionally substituted saturated or unsaturated heterocyclyl" denotes monocyclic or polycyclic heterocyclyl groups containing at least one heteroatom atom selected from nitrogen, sulphur and oxygen. Suitable heterocyclyl groups include N-containing heterocyclic groups, such as, unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl or tetrazolyl;

saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, such as, pyrrolidinyl, imidazolidinyl, piperidino or piperazinyl;

unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, such as indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl or tetrazolopyridazinyl;

unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, such as, oxiranyl, pyranyl or furyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms, such as, thienyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, oxazolyl, isoxazolyl or oxadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, morpholinyl;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, such as, benzoxazolyl or benzoxadiazolyl;

unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolyl or thiadiazolyl;

saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, thiazolidinyl; and

unsaturated condensed heterocyclic group containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, such as, benzothiazolyl or benzothiadiazolyl.

The term "carbohydrate" denotes a carbohydrate residue or a functionalised or deoxygenated carbohydrate residue, and includes monosaccharides and oligosaccharides. A carbohydrate residue is an acyclic polyhydroxy-aldehyde or ketone, or one of their cyclic tautomers, and includes a compound resulting from reduction of the aldehyde or keto group such as alditols.

Oxygen atoms may be replaced by hydrogen or bonds to a halogen, nitrogen, sulfur or carbon atoms, or carbon-oxygen bonds such as in ethers or esters may be introduced. Examples of carbohydrates include but are not limited to D-galactofuranose, *N*-acetyl-D-galactofuranose, D-glucofuranose, *N*-acetyl-D-glucofuranose, D-galactopyranose *N*-acetyl-D-galactopyranose, D-glucopyranose and *N*-acetyl-D-glucopyranose and their equivalents where oxygen atoms have been replaced in selected positions with hydrogen or bonds to halogen, nitrogen, sulfur or carbon, as well as oligosaccharides containing these moieties.

In this specification "optionally substituted" means that a group may or may not be further substituted with one or more functional groups such as alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino, benzylamino, dibenzylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, diacylamino, acyloxy, alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy, heterocyclamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy, mercapto, alkylthio, benzylthio, acylthio, phosphorus-containing groups and the like, and including groups such as oxo, =S, =N-, where appropriate, particularly as substituents in ring structures such as lactones, lactams and cyclic imides, provided that none of the substituents outlined above interferes with the formation of the subject compound.

Any of the moieties whose length is defined in terms of the number of carbon atoms present may possess any number of carbon atoms within the specified range. Nevertheless, within this range certain species will be preferred due to factors such as availability and cost of precursors and ease of synthesis, as well as efficacy. In

particular, such moieties containing 4 to 24 carbon atoms, preferably 6 to 12 carbon atoms, more preferably 8 to 10 carbon atoms and most preferably 8 carbon atoms are preferred for reasons of cost and availability of precursors, ease of synthesis and efficacy.

In an embodiment one or both of R_1 and R_2 is alkyl. In a further embodiment one or both of R_1 and R_2 is C_{4-30} alkyl, and may be C_{6-12} alkyl or C_{8-10} alkyl. Furthermore one or both of R_1 and R_2 may be aralkyl, alkyl interrupted by one or more heteroatoms or functional groups selected from the group consisting of O, S, -N=, NR_7, and $-(Y)_mC=(Z)(T)_n$, alkenyl or R_1 and R_2 together with a nitrogen atom from which they depend may form an optionally substituted saturated or unsaturated heterocyclic group, for example, a cyclic imide or a lactam. If one or both R_1 and R_2 is alkenyl it may be C_{4-30} alkenyl, in a further embodiment, C_{6-12} alkenyl and in a still further embodiment C_{8-10} alkenyl. In the case of one or both R_1 and R_2 being alkyl interrupted by one or more of heteroatoms or functional groups, the heteroatom may be oxygen, and , in an embodiment, R_1 and/or R_2 may have the formula $CH_3(CH_2)_xO(CH_2)_yO(CH_2)_z$. Equally, if one of R_3, R'_3, R''_3, R_4, R'_4, R''_4, R_5, R'_5, R''_5, R_6, R'_6, R''_6, R_7, R_8, R_9, R'_9, R_{10}, R_{11} and R'_{11} is alkyl, alkenyl, aralkyl or alkyl or alkenyl interrupted by one or more heteroatoms or functional groups, embodiments are as set out for R_1 and R_2.

In an embodiment the amine portion of the sulfenamide oxide is tethered to the carbohydrate moiety through an additional linkage. While the amine moiety may be tethered by linkage to any position in the carbohydrate moiety, linkage to the C_2 position through either R_1 or R_2 forming a ring together with X_1 is preferred. By way of example only, the linkage may take the form of an optionally substituted alkyl chain being linked to end of a functional group located in position 2 of the carbohydrate ring and linked to a functional group located within R_1 or R_2.

In an embodiment X_1 is OR_3. Advantageously R_3 is hydrogen or optionally substituted acyl.

In an embodiment X_2 is OR_4. Advantageously, R_4 is hydrogen or optionally substituted acyl.

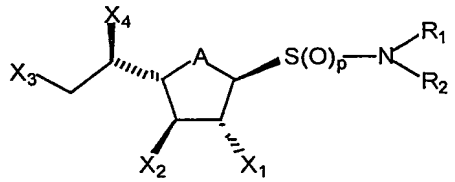
In an embodiment X_3 is OR_5. Advantageously, R_5 is hydrogen or optionally substituted acyl.

In an embodiment X_4, when present, is OR_6. Advantageously, R_6 is hydrogen or optionally substituted acyl.

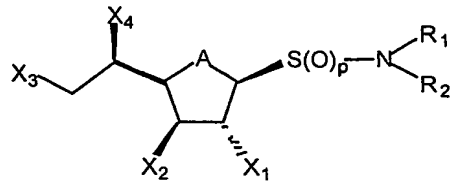
In an embodiment any one of the substituents R_3, R_4, R_5 and R_6 is optionally substituted acyl, in particular, optionally substituted acyl where the substituent on the acyl group effects the lipophilicity or water solubility of the compound. By way of example, preferred compounds include amino acid esters where the amino acid side chain is selected to provide a predetermined lipophilicity for the compound. The amino acid side chains envisaged include all of the natural occurring amino acid side chains as well as common synthetic amino acids. Alternatively, the compounds maybe succinnyl esters terminating in amides that improve water solubility.

In an embodiment p is 2 and the compounds are sulfonamides. Alternatively, p is 1 and the compounds are sulfinamides.

In a further embodiment the compounds of the invention are galactofuranosyl compounds, and therefore have the configuration illustrated in general formula (Ia):



Alternatively, the compounds of the invention are glucofuranosyl derivatives having the general formula (Ib):



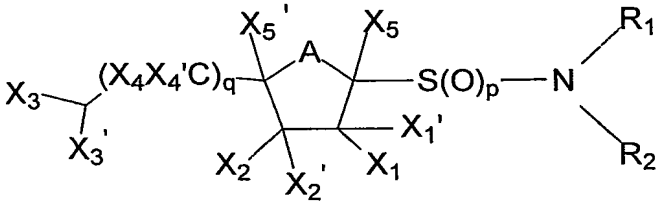
Advantageously the sulfenamide oxide of general formula (I) is selected from the oxides of group consisting of *N*,*N*-dibutyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide, *N*,*N*-dihexyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide, *N*,*N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide, *N*,*N*-didecyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide, *N*,*N*-dibenzyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide, *N*,*N*-di(2-methoxyethoxyethyl)-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfonamide, *N*,*N*-dibutyl-*S*-(β-D-galactofuranosyl)sulfenamide, *N*,*N*-dihexyl-*S*-(β-D-galactofuranosyl)sulfenamide, *N*,*N*-dioctyl-*S*-(β-D-galactofuranosyl)sulfenamide, *N*,*N*-didecyl-*S*-(β-D-galactofuranosyl)sulfenamide, *N*,*N*-dibenzyl-*S*-(β-D-galactofuranosyl)sulfenamide, *N*,*N*-di(2-methoxyethoxyethyl)-*S*-(β-D-galactofuranosyl)sulfonamide, *N*,*N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-glucofuranosyl)sulfenamide, and *N*,*N*-dioctyl-*S*-(β-D-glucofuranosyl)sulfenamide and *N*,*N*-dioctyl-*S*-(2,3-di-*O*-acetyl-5-O-[*tert*-butyldiphenylsilyl]-α-D-arabinofuranosyl)sulfonamide.

In a particularly preferred embodiment of the invention the compound of general formula (I) is an oxide of *N*,*N*-dihexyl-*S*-(β-D-galactofuranosyl)sulfenamide, *N*,*N*-dioctyl-*S*-(β-D-galactofuranosyl)sulfenamide or *N*,*N*-didecyl-*S*-(β-D-galactofuranosyl)sulfenamide, most particularly, *N*,*N*-dioctyl-*S*-(β-D-galactofuranosyl)sulfenamide.

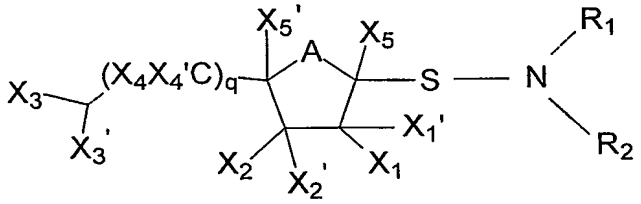
In another particularly preferred embodiment the compound of general formula (I) is an oxide of thio- (A = S) or aza- (A = NR_8) analogue of *N*,*N*-dihexyl-*S*-(β-D-galactofuranosyl)sulfenamide, *N*,*N*-dioctyl-*S*-(β-D-

galactofuranosyl)sulfenamide or *N,N*-didecyl-*S*-(β-D-galactofuranosyl)sulfenamide, most particularly of *N,N*-dioctyl-*S*-(β-D-galactofuranosyl)sulfenamide.

According to a second aspect of the present invention there is provided a method of preparation of a compound of general formula (I)



comprising reacting a compound of general formula (II):



wherein R_1, R_2, A, p, q, X_1, X_1', X_2, X_2', X_3, X_3', X_4, X_4', X_5 and X_5' are as defined above;

with an oxidising agent.

In general, X_1, X_1', X_2, X_2', X_3, X_3', X_4, X_4', X_5 and X_5', are as defined above.

Typically the oxidising agent is 3-chloroperbenzoic acid. A number of methods have been developed to oxidise sulfenamides as disclosed, for example, in Craine and Raban, 1989; Glass & Swedo, 1977; Haake, Gebbing, & Benack, 1979; the contents of which are incorporated herein by reference. In an embodiment R_2, R'_2, R''_2, R_3, R'_3, R''_3, R_4, R'_4, R''_4, R_5, R'_5, R''_5, R_6, R'_6 and R''_6 may be a protecting group, and the process includes the further step of removing the protecting groups. Protecting groups may not always be required. However, suitable protecting groups are well known to the person skilled in the art, and acetyl or benzoyl protecting groups are preferred. Acetyl and benzoyl protecting groups

are typically removed through hydrolysis with sodium methoxide in methanol. Methods for the preparation of compounds of general formula (II) are known in the art as disclosed, for example, in Craine and Raban, 1989; Koval', 1996; Owen & von Itzstein, 2000; von Itzstein *et al.*, 2003; Illyés *et al.*, 2004; the contents of which are incorporated herein by reference. An extensive array of methodologies has been developed to manipulate each position of the furanose template as disclosed, for example, in Marino, Marino, Miletti, Alves, Colli, & de Lederkremer, 1998; Miletti, Marino, Marino, de Lederkremer, Colli & Alves, 1999; Zhang & Liu, 2001; Brimacombe, Gent & Stacey, 1968; Brimacombe, Da'aboul & Tucker, 1971; Lemieux & Stick, 1975; de Lederkremer, Cirelli & Sznaidman, 1986; Shin & Perlin, 1979; de Lederkremer, Cicero & Varela, 1990; de Lederkremer, Marino & Marino, 2002; Pathak, Pathak, Suling, Gurcha, Morehouse, Besra, Maddry & Reynolds, 2002; Ernst, Hart & Sinay, 2000; the contents of which are incorporated herein by reference.

According to a third aspect of the present invention there is provided a method for the treatment of a microbial infection, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of general formula (I).

According to a fourth aspect of the present invention there is provided the use of a compound of general formula (I) in the manufacture of a medicament, particularly for use in the treatment of a microbial infection.

As used herein, the term "therapeutically effective amount" means an amount of a compound of the present invention effective to yield a desired therapeutic response, for example to prevent or treat a disease which by administration of a pharmaceutically-active agent.

The specific "therapeutically effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition and

clinical history of the subject, the type of animal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compound or its derivatives.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent, excipient or vehicle for delivering the compound of general formula (I) to the subject. The carrier may be liquid or solid, and is selected with the planned manner of administration in mind.

The compound of general formula (I) may be administered orally, topically, or parenterally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrathecal, intracranial, injection or infusion techniques.

The invention also provides suitable topical, oral, aerosol, and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compounds of the invention may be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use may contain one or more agents selected from the group of sweetening agents, flavouring agents, colouring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations. The tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets.

These excipients may be, for example, inert diluents, such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, such as corn starch or alginic acid; binding agents, such as starch, gelatin or acacia; or lubricating agents, such as magnesium stearate, stearic

acid or talc. The tablets may be uncoated, or may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time-delay material such as glyceryl monostearate or glyceryl distearate may be employed. Coating may also be performed using techniques described in the U. S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

The compound of general formula (I) of the invention can be administered, for *in vivo* application, parenterally by injection or by gradual perfusion over time independently or together. Administration may be intravenously, intra-arterial, intraperitoneally, intramuscularly, subcutaneously, intracavity, or transdermally. For *in vitro* studies the agents may be added or dissolved in an appropriate biologically acceptable buffer and added to a cell or tissue.

Preparations for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present such as, for example, anti-microbials, anti-oxidants, chelating agents, growth factors and inert gases and the like.

The compounds of general formula (I) are antimicrobial agents which are active, in particular but not limited to, against *Mycobacterium* including *Mycobacterium tuberculosis, M. avium intracellulare, M.*

fortuitum, *M. abscessus* and rapid growing atypical Mycobacterial strains, *Nocardia*, particularly *Nocardia asteroides* and *N. nova*, *Staphylococcus* including *Staphylococcus aureus* and *S. aureus* (Coagulas-negative), *Streptococcus spp.* and *Enterococci* species. The compounds of general formula (I) are particularly useful in treating infections involving these organisms.

Generally, the terms "treating", "treatment" and the like are used herein to mean affecting a subject, tissue or cell to obtain a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing infection, and/or may be therapeutic in terms of a partial or complete cure of an infection. "Treating" as used herein covers any treatment of, or prevention of infection in a vertebrate, a mammal, particularly a human, and includes: preventing the infection from occurring in a subject that may have been exposed to the infectious agent, but has not yet been diagnosed as affected; inhibiting the infection, ie., arresting its development; or relieving or ameliorating the effects of the infection, ie., cause regression of the effects of the infection.

According to a fifth aspect of the present invention there is provided a pharmaceutical composition comprising a compound of general formula (I) and a pharmaceutically acceptable carrier.

The pharmaceutical compositions according to one embodiment of the invention are prepared by bringing a compound of general formula (I) into a form suitable for administration to a subject using carriers, excipients and additives or auxiliaries.

Frequently used carriers or auxiliaries include magnesium carbonate, titanium dioxide, lactose, mannitol and other sugars, talc, milk protein, gelatin, starch, vitamins, cellulose and its derivatives, animal and vegetable oils, polyethylene glycols and solvents, such as sterile water, alcohols, glycerol and polyhydric alcohols. Intravenous vehicles include fluid and nutrient

replenishers. Preservatives include antimicrobial, anti-oxidants, chelating agents and inert gases. Other pharmaceutically acceptable carriers include aqueous solutions, non-toxic excipients, including salts, preservatives, buffers and the like, as described, for instance, in Remington's Pharmaceutical Sciences, 15th ed. Easton: Mack Publishing Co., 1405-1412,1461-1487 (1975) and The National Formulary XIV., 14th ed. Washington: American Pharmaceutical Association (1975), the contents of which are hereby incorporated by reference. The pH and exact concentration of the various components of the pharmaceutical composition are adjusted according to routine skills in the art. See Goodman and Gilman's The Pharmacological Basis for Therapeutics (7th ed.).

The pharmaceutical compositions are preferably prepared and administered in dosage units. Solid dosage units include tablets, capsules and suppositories. For treatment of a subject, depending on activity of the compound, manner of administration, nature and severity of the disorder, age and body weight of the subject, different daily doses can be used. Under certain circumstances, however, higher or lower daily doses may be appropriate. The administration of the daily dose can be carried out both by single administration in the form of an individual dose unit or else several smaller dose units and also by multiple administration of subdivided doses at specific intervals.

The pharmaceutical compositions according to the invention may be administered locally or systemically in a therapeutically effective dose. Amounts effective for this use will, of course, depend on the severity of the microbial infection and the weight and general state of the subject. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in situ* administration of the pharmaceutical composition, and animal models may be used to determine effective dosages for treatment of the cytotoxic side effects. Various considerations are described, eg., in Langer, Science,

249: 1527, (1990). Formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspension. Such excipients may be suspending agents such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents, which may be (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylenoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as those mentioned above. The sterile injectable preparation may also a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents which may be employed are water, Ringer's solution, and isotonic sodium chloride solution.

In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of general formula (I) may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. Compounds of general formula (I) may also be administered in combination with cyclodextrins for enhanced aqueous solubility.

Dosage levels of the compound of general formula (I) of the present invention will usually be of the order of about 0.05mg to about 20mg per kilogram body weight, with a preferred dosage range between about 0.05mg to about 10mg per kilogram body weight per day (from about 0.1g to about 3g per patient per day). The amount of active ingredient which may be combined with the carrier materials to produce a single dosage will vary, depending upon the host to be treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain about 1mg to 1g of an active compound with an appropriate and convenient amount of carrier material, which may vary from about 5 to 95 percent of the total composition. Dosage unit forms will generally contain between from about 5mg to 500mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In addition, some of the compounds of the invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The compounds of the invention may additionally be combined with other compounds to provide an operative combination. It is intended to include any chemically compatible combination of pharmaceutically-active agents, as long as the combination does not eliminate the activity of the compound of general formula (I) of this invention.

According to a sixth aspect of the present invention there is provided a method of killing a microorganism, comprising exposing said microorganism to a compound of general formula (I) as defined above.

Advantageously, although not limited to, the microorganism is selected from the group consisting of *Mycobacterium* including *Mycobacterium tuberculosis*, *M. avium intracellulare*, *M. fortuitum*, *M. abscessus* and rapid growing atypical Mycobacterial strains, *Nocardia*, particularly *Nocardia asteroides* and *N. nova*, *Staphylococcus* including *Staphylococcus aureus* and *S. aureus* (Coagulas-negative), *Streptococcus spp.* and *Enterococci* species.

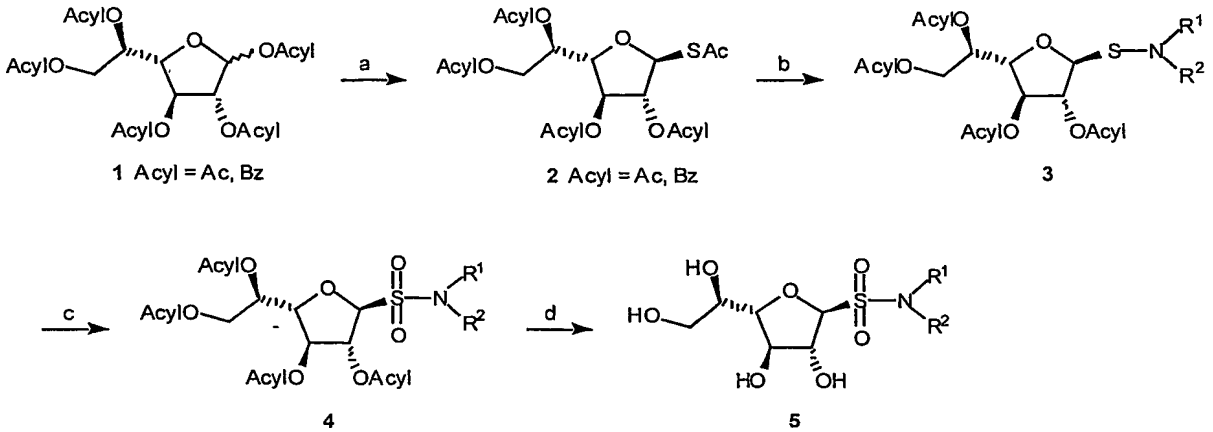
Throughout this specification and the claims, the words "comprise", "comprises" and "comprising" are used in a non-exclusive sense, except where the context requires otherwise.

It will be clearly understood that, although a number of prior art publications are referred to herein, this reference does not constitute an admission that any of these documents forms part of the common general knowledge in the art, in Australia or in any other country.

Modes for Performing the Invention

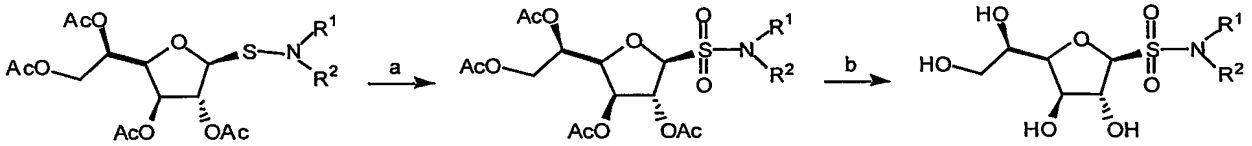
The synthetic schemes employed to prepare compounds in accordance with preferred embodiments of the invention are now described in more detail. The synthesis

of protected (compounds 4; Examples 1 to 6) and deprotected (compounds 5; Examples 9 to 14) galactofuranosyl sulfonamides is shown in Scheme 1. For the preparation of these examples, 1,2,3,5,6-penta-*O*-acetyl-D-galactofuranose (compound 1, Acyl = acetyl; Bakinovskii *et al.*, 1988) and 1-*S*-acetyl-2,3,5,6-tetra-*O*-benzoyl-1-thio-β-D-galactofuranose (compound 2, Acyl = benzoyl; Owen and von Itzstein, 2000) were prepared according to known literature methods and are shown in Scheme 1 without modification. The synthesis of protected (compound 7; Example 7) and deprotected (compound 8; Example 15) glucofuranosyl sulfonamides is shown in Scheme 2. The synthesis of a protected (compound 13; Example 8) arabinofuranosyl sulfonamide is shown in Scheme 3. For the preparation of these examples, 5-*O*-(*t*-butyldiphenylsilyl)-D-arabinofuranose (compound 9) was prepared according to known literature methods and is shown in Scheme 2 without modification. The synthesis of a protected (compound 15, Example 16) and deprotected (compound 16, Example 17) glucofuranosyl sulfonamides is shown in Scheme 4. All new compounds gave the expected spectroscopic data.



Scheme 1

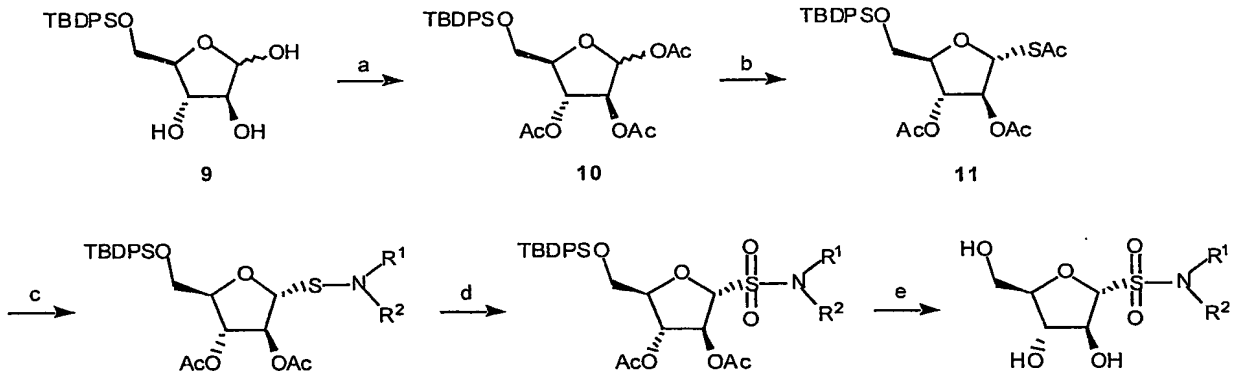
Reagents and Conditions: a) $SnCl_4$ or $BF_3.Et_2O$, HSAc, CH_2Cl_2, 0 °C to rt, 1 to 6 h, N_2; b) $BrCH(COOEt)_2$, HNR^1R^2, DMF, THF, or MeOH, rt, 4 h to 7 d; c) MCPBA, CH_2Cl_2, reflux, 1-4 h; d) NaOMe, MeOH, rt, 2 h, N_2.



6 $R^1 = R^2 = C_8H_{17}$ 7 $R^1 = R^2 = C_8H_{17}$ 8 $R^1 = R^2 = C_8H_{17}$

Scheme 2

Reagents and Conditions: a) MCPBA, CH_2Cl_2, reflux, 4 h; b) NaOMe, MeOH, rt, 2 h, N_2.

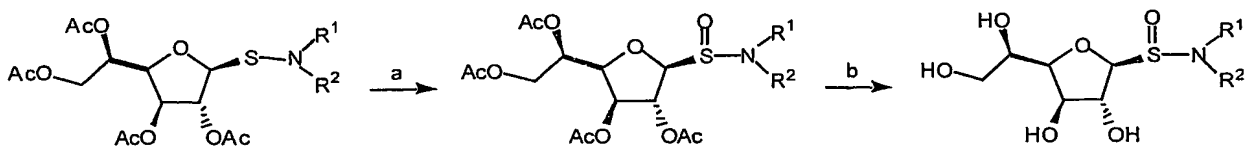


9 10 11

12 $R^1 = R^2 = C_8H_{17}$ 13 $R^1 = R^2 = C_8H_{17}$ 14 $R^1 = R^2 = C_8H_{17}$

Scheme 3

Reagents and Conditions: a) pyridine, Ac_2O, 0 °C, 1 h, N_2; b) $BF_3.Et_2O$, CH_2Cl_2, HSAc, rt, 5 h, Ar; c) $BrCH(COOEt)_2$, $HN(C_8H_{17})_2$, MeOH, rt, 3 h, Ar; d) MCPBA, CH_2Cl_2, reflux, 4 h; e) i. TBAF, AcOH, THF, rt, 6 h, N_2; ii. NaOMe, MeOH, rt, 2 h, N_2.



6 $R^1 = R^2 = C_8H_{17}$ 15 $R^1 = R^2 = C_8H_{17}$ 16 $R^1 = R^2 = C_8H_{17}$

Scheme 4

Reagents and Conditions: a) i. *N*-chlorosuccinimide, CH_2Cl_2, 0 °C, 30 min; ii. $H_2O/KHCO_3$, According to Haake *et al.*, 1979; b) NaOMe, MeOH, rt, 2 h, N_2.

General procedure for the preparation of sulfenamides; exemplified for reaction of 1-S-acetyl-2,3,5,6-tetra-O-acetyl-1-thio-β-D-galactofuranose (2, Acyl = acetyl):

To a solution of 1-*S*-acetyl-2,3,5,6-tetra-*O*-acetyl-1-thio-β-D-galactofuranose (2) (2.0 g) in solvent (60 mL) is added diethyl bromomalonate (1.5 equiv.) and amine (3 equiv.), and the reaction is stirred at room temperature. Upon completion of the reaction the volatile compounds are removed under reduced pressure and the residue is chromatographed on silica.

General procedure for the oxidation of sulfenamides to the corresponding sulfonamides:

To a solution of the protected sulfenamide (0.5 mmol) in dichloromethane (20 mL) is added *meta*-chloroperoxybenzoic acid (3 equiv.) and the mixture is heated under reflux. Upon completion of the reaction, the reaction mixture is diluted to 50 mL with dichloromethane and quenched with saturated aqueous sodium hydrogen carbonate (20 mL). The organic phase is separated and dried (Na_2SO_4), filtered, concentrated under reduced pressure, and the residue is chromatographed on silica.

Example 1

N,N-Dibutyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = C_4H_9$):

Prepared according to the general procedure by reaction of 1-*S*-acetyl-2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranose (2) with diethyl bromomalonate and dibutylamine in dry DMF for 23 h, at room temperature

under Ar. The residue was chromatographed on silica (6:1 hexanes/EtOAc) to furnish *N,N*-dibutyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl) sulfenamide (39%). R_f 0.26 (2:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (6H, t, 2 x CH_3), 1.22-1.34 (4H, m, 2 x CH_2), 1.52-1.62 (4H, m, 2 x CH_2), 2.91-3.00 (4H, m, 2 x CH_2), 4.68-4.82 (3H, m, H-4, H-6, H-6′), 5.30 (1H, dd, $J_{2,3}$ 2.4, $J_{2,1}$ 3.0 Hz, H-2), 5.67 (1H, dd, $J_{3,2}$ 2.1, $J_{3,4}$ 5.1 Hz, H-3), 5.78 (1H, d, $J_{1,2}$ 3.0 Hz, H-1), 6.05-6.09 (1H, m, H-5), 7.28-7.61 (12H, m, *m,p* Ar-H), 7.87-7.98 (m, 4H, *o* Ar-H), 8.03-8.11 (m, 4H, *o* Ar-H).

N,N-Dibutyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfonamide (4, $R^1 = R^2 = C_4H_9$):

Prepared from *N,N*-dibutyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = C_4H_9$) according to the general procedure. Yield: 75%. R_f 0.24 (4:1, hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (6H, t, 2 x CH_3), 1.18-1.31 (4H, m, 2 x CH_2), 1.47-1.59 (4H, m, 2 x CH_2), 3.15-3.35 (4H, m, 2 x CH_2), 4.65-4.76 (2H, m, H-6, H-6′), 5.06 (1H, dd, $J_{4,5}$ 4.5, $J_{4,3}$ 5.4 Hz, H-4), 5.19 (1H, d, $J_{1,2}$ 2.1 Hz, H-1), 5.78 (1H, dd, $J_{3,2}$ 2.1, $J_{3,4}$ 5.4 Hz, H-3), 6.00 (1H, m, H-5), 6.22 (1H, t, $J_{2,1} = J_{2,3}$ 2.1 Hz, H-2), 7.29-7.60 (m, 12H, *m,p* Ar-H), 7.89-7.96 (m, 4H, *o* Ar-H), 8.04-8.12 (m, 4H, *o* Ar-H).

Example 2

N,N-Dihexyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = C_6H_{13}$):

Prepared according to the general procedure by reaction of 1-*S*-acetyl-2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranose (2) with diethyl bromomalonate and dihexylamine in methanol for 4 h at room temperature. The residue was chromatographed on silica (3:1 hexanes/EtOAc) to furnish *N,N*-dihexyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl) sulfenamide (56%). R_f 0.29 (3:1 hexanes/EtOAc).

N,*N*-Dihexyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfonamide (4, $R^1 = R^2 = C_6H_{13}$):

Prepared from *N*,*N*-dihexyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = C_6H_{13}$) according to the general procedure. Yield: 60%. R_f 0.27 (3:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (6H, t, 2 x CH_3), 1.23-1.37 (12H, m, 6 x CH_2), 1.55-1.63 (4H, m, 2 x CH_2), 2.05, 2.09, 2.11, 2.13 (4 x 3H, 4 x s, 4 x OAc), 3.12-3.30 (4H, m, 2 x CH_2), 4.17 (1H, dd, $J_{6,5}$ 6.9, $J_{6,6'}$ 11.7 Hz, H-6), 4.27 (1H, dd, $J_{6',5}$ 5.1, $J_{6',6}$ 11.4 Hz, H-6'), 4.61 (1H, dd, $J_{4,5}$ 3.6, $J_{4,3}$ 7.5 Hz, H-4), 4.82 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 5.18 (1H, dd, $J_{3,2}$ 3.9, $J_{3,4}$ 7.5 Hz, H-3), 5.27 (1H, m, H-5), 5.84 (1H, t, $J_{2,1} = J_{2,3}$ 3.9 Hz, H-2).

Example 3

N,*N*-Dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfonamide (4, $R^1 = R^2 = C_8H_{17}$):

Prepared from *N*,*N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = C_8H_{17}$; von Itzstein *et al.*, 2003) according to the general procedure. Yield: 77%. R_f 0.62 (3:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 - 8.13 (m, 20 H, 4 x CO_2Ph), 6.22 (app t, 1 H, *J* 2.2 Hz, H-2), 5.99 (m, 1 H, H-5), 5.78 (dd, 1 H, $J_{3,4}$ 5.4, $J_{3,2}$ 2.0 Hz, H-3), 5.19 (d, 1 H, $J_{1,2}$ 2.1 Hz, H-1), 5.06 (dd, 1 H, $J_{4,5}$ 4.4, $J_{4,3}$ 5.3 Hz, H-4), 4.65-4.77 (m, 2 H, H-6 and H-6'), 3.12-3.37 (m, 4 H, $N(CH_2)_2$), 1.53 (m, 4 H, 2 x CH_2, dioctyl chain), 1.14-1.32 (m, 20 H, 10 x CH_2, dioctyl chain), 0.86 (app t, 6 H, *J* 6.5, *J* 6.9 Hz, 2 x CH_3); LRMS (ESI): $^m/_z$ 906 [(M + Na)$^+$ 100%].

Example 4

N,*N*-Didecyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = C_{10}H_{21}$):

Prepared according to the general procedure by reaction of 1-*S*-acetyl-2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranose (2) with diethyl bromomalonate and

didecylamine in methanol for 4 h at room temperature. The residue was chromatographed on silica (10:1 to 4:1 hexanes/EtOAc) to furnish *N,N*-didecyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl) sulfenamide (74%). R_f 0.38 (3:1 hexanes/EtOAc).

N,N-Didecyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfonamide (4, $R^1 = R^2 = C_{10}H_{21}$):

Prepared from *N,N*-didecyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = C_{10}H_{21}$) according to the general procedure. Yield: 64%. R_f 0.34 (3:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (6H, t, 2 x CH_3), 1.19-1.37 (28H, m, 14 x CH_2), 1.49-1.65 (4H, m, 2 x CH_2), 2.05, 2.08, 2.10, 2.13 (4 x 3H, 4 x s, 4 x OAc), 3.11-3.31 (4H, m, 2 x CH_2), 4.17 (1H, dd, $J_{6,5}$ 6.9, $J_{6,6'}$ 11.4 Hz, H-6), 4.27 (1H, dd, $J_{6',5}$ 5.1, $J_{6',6}$ 11.4 Hz, H-6'), 4.61 (1H, dd, $J_{4,5}$ 3.6, $J_{4,3}$ 7.5 Hz, H-4), 4.82 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 5.18 (1H, dd, $J_{3,2}$ 4.2, $J_{3,4}$ 7.5 Hz, H-3), 5.27 (1H, m, H-5), 5.83 (1H, t, $J_{2,1} = J_{2,3}$ 3.9 Hz, H-2).

Example 5

N,N-Dibenzyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = CH_2Ph$):

Prepared according to the general procedure by reaction of 1-*S*-acetyl-2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranose (2) with diethyl bromomalonate and dibenzylamine in dry THF for 7 days, at room temperature under Ar. The residue was chromatographed on silica (4:1 hexanes/EtOAc) to furnish *N,N*-dibenzyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfenamide (16%) as a pale orange syrup. R_f 0.41 (4:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-8.20 (m, 30 H, 4 x CO_2Ph and $N(CH_2)_2$(Ph)$_2$), 6.05 (m, 1 H), 5.97 (dd, 1 H, *J* 3.4, *J* 6.5 Hz), 5.76 (d, 1 H, *J* 3.6 Hz), 5.65 (bd, 1 H, *J* 4.7 Hz), 5.49 (m, 2 H), 5.35 (d, 1 H, *J* 6.6 Hz), 4.71 (m, 3 H), 4.58 (app t, 1 H, *J* 3.2 Hz), 4.19-4.40 (m, 5 H), 3.83 (d,

2 H, *J* 14.3 Hz); LRMS (ESI): $^{m}/_{z}$ 830 [(M + Na)$^{+}$ 100%], 357 (60), 198 (58), 808 (41).

N,N-Dibenzyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl)sulfonamide (4, $R^1 = R^2 = CH_2Ph$):

Prepared from *N,N*-dibenzyl-*S*-(2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranosyl) sulfenamide (3, $R^1 = R^2 = CH_2Ph$) according to the general procedure. Yield: 52%. R_f 0.45 (hexane-EtOAc 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-8.15 (m, 30 H, 4 x $CO_2\underline{Ph}$ and $N(CH_2\underline{Ph})_2$), 6.30 (app t, 1 H, *J* 2.2 Hz, H-2), 6.01 (m, 1 H, H-5), 5.80 (dd, 1 H, $J_{3,4}$ 5.4, $J_{3,2}$ 2.1 Hz, H-3), 5.13 (m, 1 H, H-4), 5.11 (d, 1 H, $J_{1,2}$ 2.3 Hz, H-1), 4.69 (d, 2 H, *J* 5.9 Hz, H-6 and H-6'), 4.49 (d, 2 H, *J* 15.4 Hz, $N(C\underline{H}_2Ph)_2$), 4.31 (d, 2 H, *J* 15.4 Hz, $N(C\underline{H}_2Ph)_2$); LRMS (ESI): $^{m}/_{z}$ 862 [(M + Na)$^{+}$ 100%]; Anal. Calcd for $C_{48}H_{41}NO_{11}S$: C, 68.84; H, 4.92; N, 1.67. Found: C, 68.50; H, 4.96; N, 1.58.

Example 6

N,N-Di(2-methoxyethoxyethyl)-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = CH_2CH_2OCH_2CH_2OCH_3$):

Prepared according to the general procedure by reaction of 1-*S*-acetyl-2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranose (2) with diethyl bromomalonate and *N,N*-di(2-methoxyethoxyethyl)amine in methanol for 19 h at room temperature. The residue was chromatographed on silica (EtOAc) to furnish *N,N*-(2-methoxyethoxyethyl)-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide (72%) as a light golden oil. R_f 0.32 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.91, 1.93, 1.96, 1.99 (4 x 3H, 4 x s, 4 x OAc), 3.08 (4H, t, *J* = 6 Hz, NCH_2CH_2), 3.23 (6H, s, OMe), 3.30-3.60 (12H, m, OCH_2), 4.00-4.25 (3H, m, H-5, H-6, H-6`), 4.92 (2H, m, H-2, H-3), 5.19 (1H, m, H-5), 5.29 (1H, d, $J_{1,2}$ 3.3 Hz, H-1).

N,N-Di(2-methoxyethoxyethyl)-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfonamide (4, $R^1 = R^2 = CH_2CH_2OCH_2CH_2OCH_3$):

Prepared from *N,N*-di(2-methoxyethoxyethyl)-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranosyl)sulfenamide (3, $R^1 = R^2 = CH_2CH_2OCH_2CH_2OCH_3$) according to the general procedure (reaction for 1 h). Yield: 76%. R_f 0.24 (ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95, 1.97, 1.99, 2.01 (4 x 3H, 4 x s, 4 x OAc), 3.29 (6H, s, OMe), 3.40-3.70 (16H, m, OEt), 4.10-4.25 (2H, m, H-6, H-6`), 4.53 (2H, dd, $J_{3,4}$ 7.8, $J_{4,5}$ 3.6 Hz, H-4), 5.10 (1H, dd, $J_{2,3}$ 4.2, $J_{4,5}$ 3.6 Hz, H-3), 5.18 (1H, m, H-5), 5.28 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 5.75 (1H, dd, $J_{1,2}$ 3.6, $J_{2,3}$ 4.2 Hz, H-2).

Example 7

N,N-Dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-glucofuranosyl)sulfonamide (7, $R^1 = R^2 = C_8H_{17}$):

Prepared from *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-glucofuranosyl)sulfenamide (6, $R^1 = R^2 = C_8H_{17}$; von Itzstein *et al.*, 2003) according to the general procedure. Yield: 39%. R_f 0.21 (3:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (6H, t, 2 x CH_3), 1.22-1.34 (20H, m, 10 x CH_2), 1.51-1.64 (4H, m, 2 x CH_2), 2.00, 2.08, 2.09, 2.13 (4 x 3H, 4 x s, 4 x OAc), 3.14-3.33 (4H, m, 2 x CH_2), 4.13 (1H, dd, $J_{6,5}$ 4.8, $J_{6,6'}$ 12.3 Hz, H-6), 4.39 (1H, dd, $J_{4,3}$ 4.2, $J_{4,5}$ 9.0 Hz, H-4), 4.56 (1H, dd, $J_{6',5}$ 2.1, $J_{6',6}$ 12.3 Hz, H-6'), 4.77 (1H, d, $J_{1,2}$ 2.7 Hz, H-1), 5.31-5.37 (2H, m, H-3, H-5), 5.56 (1H, app. d, $J_{2,1} \sim J_{2,3}$ 2.1 Hz, H-2).

Example 8

1,2,3-Tri-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-α/β-D-arabinofuranose (10):

5-*O*-(*Tert*-butyldiphenylsilyl)-α/β-D-arabinose (9) (2.10 g, 5.40 mmol) was dissolved in dry pyridine (20 mL) and stirred with acetic anhydride (20 mL, excess) under N_2 at 0 °C for 1 h and then at room temperature for 18 h. After this time the solvent removed under reduced pressure and the residue was chromatographed on silica

(4:1 hexanes/EtOAc) to furnish 1,2,3-tri-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-α/β-D-arabinofuranose (2.67 g, 96%) as a clear syrup. R_f 0.45 (4:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.22 (m, 10 H, SiPh), 6.37 (d, 1 H, $J_{1,2}$ 4.7 Hz, H-1β), 6.19 (bs, 1 H, H-1α), 5.63 (dd, 1 H, $J_{3,4}$ 6.1, $J_{3,2}$ 7.2 Hz, H-3β), 5.38 (m, 1 H, H-3α), 5.33 (dd, 1 H, $J_{2,1}$ 4.8, $J_{2,3}$ 7.2 Hz, H-2β), 5.21 (app d, 1 H, *J* 1.6 Hz, H-2α), 4.24 (dd, 1 H, *J* 4.0, *J* 8.8 Hz, H-4α), 4.12 (m, 1 H, H-4β), 3.87 (m, 2 H, H-5α and H-5'α), 3.81 (m, 2 H, H-5β and H-5'β), 2.02-2.13 (6 x s, 18 H, 6 x OAc α and β), 1.07 (bs, 18 H, *tert*-butyl α and β).

1-*S*-Acetyl-2,3-di-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-1-thio-α-D-arabinofuranose (11):

To a solution of 1,2,3-tri-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-α/β-D-arabinofuranose (10) (2.10 g, 4.08 mmol) in dry DCM (20 mL) at 0 °C, under Ar was added $BF_3.OEt_2$ (1.2 equivalents, 4.90 mmol). After 10 minutes thiolacetic acid (1.5 equivalents, 4.33 mL, 6.12 mmol) was added and the reaction was stirred for 5 h at room temperature under Ar. After this time the reaction was diluted with EtOAc (150 mL) and sat. aq. $NaHCO_3$ (150 mL). The layers were separated and the organic layer was washed once with sat. aq. $NaHCO_3$ (150 mL) and once with aq. NaCl (150 mL). The organic phase was then dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The residue was chromatographed on silica (3:1 hexanes/EtOAc) to furnish 1-*S*-acetyl-2,3-di-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-1-thio-α-D-arabinofuranose (1.88 g, 87%) as a clear syrup. R_f 0.30 (4:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.73 (m, 4 H, Si(Ph)$_2$), 7.34-7.46 (m, 6 H, Si(Ph)$_2$), 6.00 (bs, 1 H, H-1), 5.37 (m, 1 H, H-2), 5.25 (app t, 1 H, *J* 1.6 Hz, H-3), 4.14 (m, 1 H, H-4), 3.85 (m, 2 H, H-5 and H-5'), 2.39 (s, 3 H, SCOCH$_3$), 2.11 (s, 3 H, 1 x OCOCH$_3$), 2.02 (s, 3 H, 1 x OCOCH$_3$), 1.06 (s, 9 H, -C(CH$_3$)$_3$).

N,N-Dioctyl-*S*-(2,3-di-*O*-acetyl-5-O-[*tert*-butyldiphenylsilyl]-α-D-arabinofuranosyl)sulfenamide (12, $R^1 = R^2 = C_8H_{17}$):

Prepared according to the general procedure by reaction of 1-*S*-acetyl-2,3-di-*O*-acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-1-thio-α-D-arabinofuranose (11) with diethyl bromomalonate and dioctylamine in dry methanol for 3 h, at room temperature under Ar. The residue was chromatographed on silica (6:1 hexanes/EtOAc) to furnish *N,N*-dioctyl-*S*-(2,3-di-*O*-acetyl-5-*O*-[*tert*-butyldiphenylsilyl]-α-D-arabinofuranosyl)sulfenamide (64%) as a pale yellow syrup. R_f 0.70 (4:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.73 (m, 4 H, Si(Ph)$_2$), 7.33-7.47 (m, 6 H, Si(Ph)$_2$), 5.44 (d, 1 H, $J_{1,2}$ 4.1 Hz, H-1), 5.34 (dd, 1 H, $J_{3,4}$ 5.4, $J_{3,2}$ 3.2 Hz, H-3), 5.12 (dd, 1 H, $J_{2,3}$ 3.2, $J_{2,1}$ 4.0 Hz, H-2), 4.22 (m, 1 H, H-4), 3.85 (d, 2 H, J 3.9 Hz, H-5 and H-5′), 2.90 (m, 4 H, N(CH$_2$)$_2$), 2.05 (s, 6 H, 2 x OCOCH$_3$), 1.18-1.63 (m, 24 H, 12 x CH_2 dioctyl chain), 1.06 (s, 9 H, -C(CH$_3$)$_3$), 0.87 (m, 6 H, 2 x CH_3).

N,N-Dioctyl-*S*-(2,3-di-*O*-acetyl-5-O-[*tert*-butyldiphenylsilyl]-α-D-arabinofuranosyl)sulfonamide (13, $R^1 = R^2 = C_8H_{17}$):

Prepared from *N,N*-dioctyl-*S*-(2,3-di-*O*-acetyl-5-*O*-[*tert*-butyldiphenylsilyl]-α-D-arabinofuranosyl)sulfenamide (12, $R^1 = R^2 = C_8H_{17}$) according to the general procedure. Yield: 53%. R_f 0.61 (4:1 hexanes/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.71 (m, 4 H, Si(Ph)$_2$), 7.34-7.47 (m, 6 H, Si(Ph)$_2$), 5.85 (app t, 1 H, J 3.4 Hz, H-2), 5.43 (dd, 1 H, $J_{3,4}$ 6.9, $J_{3,2}$ 3.6 Hz, H-3), 4.85 (d, 1 H, $J_{1,2}$ 3.3 Hz, H-1), 4.48 (m, 1 H, H-4), 3.83 (m, 2 H, H-5 and H-5′), 3.11-3.37 (m, 4 H, N(CH$_2$)$_2$), 2.08 (s, 3 H, 1 x OCOCH$_3$), 2.07 (s, 3 H, 1 x OCOCH$_3$), 1.51-1.68 (m, 4 H, 2 x CH_2 dioctyl chain), 1.17-1.39 (m, 20 H, 10 x CH_2 dioctyl chain), 1.06 (s, 9 H, -C(CH$_3$)$_3$), 0.87 (m, 6 H, 2 x CH_3).

General procedure for the deprotection of benzoate and acetate protecting groups:

To a solution of the protected sulfonamide (0.5 mmol) in dry methanol (10 mL) under an atmosphere of N_2 was added one equivalent of sodium methoxide (1M solution in dry methanol). The reaction was left to stir at room temperature for 2 h. After this time the reaction was neutralized with Amberlite (H^+) resin. The resin was removed by filtration and the solvent removed under reduced pressure. The residue was chromatographed on silica to yield the desired deprotected compound.

*General procedure for the deprotection of tert-*butyldiphenylsilyl *protecting groups*:

To a solution of the silyl protected sulfonamide (0.5 mmol) in dry THF (5 mL) under an atmosphere of N_2 is added one and a half equivalents of tetrabutylammonium fluoride (1 M solution in THF) and acetic acid (0.1 mL). The reaction is left to stir at room temperature for 15 h, then additional acetic acid (0.5 mL) is added and the reaction is left to stir for a further 1 h. After this time the reaction mixture is evaporated under reduced pressure. The residue is chromatographed on silica to yield the desired desilylated compound.

Example 9

N,*N*-Dibutyl-*S*-(β-D-galactofuranosyl)sulfonamide (5, $R^1 = R^2 = C_4H_9$):

Yield: 80%. R_f 0.36 (15:1 EtOAc/MeOH). ^1H NMR (300 MHz, CD_3OD): δ 0.98 (6H, t, 2 x CH_3), 1.30-1.43 (4H, m, 2 x CH_2), 1.56-1.67 (4H, m, 2 x CH_2), 3.24-3.39 (4H, m, 2 x CH_2), 3.60-3.76 (3H, m, H-6, H-6′, H-5), 4.07 (1H, dd, $J_{4,5}$ 2.4, $J_{4,3}$ 8.7 Hz, H-4), 4.17 (1H, dd, $J_{3,2}$ 6.0, $J_{3,4}$ 8.7 Hz, H-3), 4.55 (1H, dd, $J_{2,1}$ 5.1, $J_{2,3}$ 6.0 Hz, H-2), 4.69 (1H, d, $J_{1,2}$ 5.1 Hz, H-1).

Example 10

N,*N*-Dihexyl-*S*-(β-D-galactofuranosyl)sulfonamide (5, $R^1 = R^2 = C_6H_{13}$):

Yield: 78%. R_f 0.24 (EtOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 0.92 (6H, t, 2 x CH_3), 1.27-1.40 (12H, m, 6 x CH_2), 1.53-1.66 (4H, m, 2 x CH_2), 3.16-3.36 (4H, m, 2 x CH_2), 3.55-3.73 (3H, m, H-6, H-6', H-5), 4.05 (1H, dd, $J_{4,5}$ 2.4, $J_{4,3}$ 8.7 Hz, H-4), 4.15 (1H, dd, $J_{3,2}$ 6.3, $J_{3,4}$ 8.7 Hz, H-3), 4.52 (1H, dd, $J_{2,1}$ 5.1, $J_{2,3}$ 6.3 Hz, H-2), 4.66 (1H, d, $J_{1,2}$ 5.1 Hz, H-1).

Example 11

N,*N*-Dioctyl-*S*-(β-D-galactofuranosyl)sulfonamide (5, $R^1 = R^2 = C_8H_{17}$):

Yield: 75%. R_f 0.58 (EtOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 4.58 (d, 1 H, *J* 5.2 Hz, H-1), 4.44 (dd, 1 H, $J_{2,3}$ 6.1, $J_{2,1}$ 5.2 Hz, H-2), 4.06 (dd, 1 H, $J_{3,4}$ 8.7, $J_{3,2}$ 6.1 Hz, H-3), 3.96 (dd, 1 H, $J_{4,5}$ 2.4, $J_{4,3}$ 8.7 Hz, H-4), 3.62 (m, 1 H, H-5), 3.52 (m, 2 H, H-6 and H-6'), 3.20 (m, 4 H, $N(CH_2)_2$), 1.52 (m, 4 H, 2 x CH_2, dioctyl chain), 1.23 (m, 20 H, 10 x CH_2, dioctyl chain), 0.82 (app t, 6 H, *J* 6.5, *J* 6.9 Hz, 2 x CH_3); LRMS (ESI): $^m/_z$ 490 [(M + Na)$^+$ 100%]; Anal. Calcd for $C_{22}H_{45}NO_7S.^1/_2\ H_2O$: C, 55.43; H, 9.73; N, 2.94. Found: C, 55.75; H, 10.07; N, 2.80.

Example 12

N,*N*-Didecyl-*S*-(β-D-galactofuranosyl)sulfonamide (5, $R^1 = R^2 = C_{10}H_{21}$):

Yield: 89%. R_f 0.31 (EtOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 0.91 (6H, t, 2 x CH_3), 1.26-1.38 (28H, m, 14 x CH_2), 1.54-1.66 (4H, m, 2 x CH_2), 3.21-3.36 (4H, m, 2 x CH_2), 3.55-3.73 (3H, m, H-6, H-6', H-5), 4.05 (1H, dd, $J_{4,5}$ 2.4, $J_{4,3}$ 8.7 Hz, H-4), 4.15 (1H, dd, $J_{3,2}$ 6.3, $J_{3,4}$ 9.0 Hz, H-3), 4.53 (1H, dd, $J_{2,1}$ 5.4, $J_{2,3}$ 6.0 Hz, H-2), 4.67 (1H, d, $J_{1,2}$ 5.1 Hz, H-1).

Example 13

N,*N*-Dibenzyl-*S*-(β-D-galactofuranosyl)sulfonamide (5, $R^1 = R^2 = CH_2Ph$):

Yield: 76%. R_f 0.42 (EtOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 7.17-7.32 (m, 10 H, $N(CH_2\underline{Ph})_2$), 4.75 (d, 1 H, *J* 5.0 Hz, H-1), 4.64 (m, 1 H, , H-2), 4.47 (d, 2 H, *J* 15.4 Hz, 1 x $N(C\underline{H}_2Ph)_2$), 4.31 (d, 2 H, *J* 15.5 Hz, 1 x $N(C\underline{H}_2Ph)_2$), 4.15-4.22 (m, 2 H, H-3 and H-4), 3.73 (app dt, 1 H, *J* 2.0, *J* 6.5 Hz, H-5), 3.58-3.63 (m, 2 H, H-6 and H-6'); LRMS (ESI): $^m/_z$ 446 [(M + Na)$^+$ 100%]; Anal. Calcd for $C_{20}H_{25}NO_7S$: C, 56.72; H, 5.95; N, 3.31. Found: C, 56.33; H, 6.01; N, 3.10.

Example 14

N,N-Di(2-methoxyethoxyethyl)-*S*-(β-D-galactofuranosyl)sulfonamide (5, $R^1 = R^2 = CH_2CH_2OCH_2CH_2OCH_3$):

Yield: 87%. R_f 0.39 (14:5:1 EtOAc/methanol/H_2O). ^{1}H NMR (300 MHz, D_2O): δ 3.37 (6H, s, OMe), 3.49 (1H, m, H-6), 3.50-3.75 (16H, overlapping m, OCH_2), 3.75 (1H, m, H-6~), 3.82 (1H, m, H-5), 4.08 (1H, dd, $J_{3,4}$ 9.0 Hz, $J_{2,3}$ 6.3 Hz, H-4), 4.19 (1H, dd, $J_{2,3}$ 6.3 Hz, $J_{3,4}$ 9.0 Hz, H-3) , 4.61 (1H, dd, $J_{1,2}$ 5.4 Hz, $J_{2,3}$ 6.6 Hz, H-2), 5.07 (1H, d, $J_{1,2}$ 5.4 Hz, H-1); LRMS (ESI): *m/z* 470.9 [(M + Na)$^+$, 100%).

Example 15

N,N-Dioctyl-*S*-(β-D-glucofuranosyl)sulfonamide (8, $R^1 = R^2 = C_8H_{17}$):

Yield: 55%. R_f 0.05 (1:1 Hexanes/EtOAc). ^{1}H NMR (300 MHz, CD_3OD): δ 0.88 (6H, t, 2 x CH_3), 1.21-1.37 (20H, m, 10 x CH_2), 1.50-1.64 (4H, m, 2 x CH_2), 3.13-3.35 (4H, m, 2 x CH_2), 3.59 (1H, dd, $J_{6,5}$ 5.4, $J_{6,6'}$ 11.4 Hz, H-6), 3.75 (1H, dd, $J_{6',5}$ 2.7, $J_{6',6}$ 11.7 Hz, H-6'), 3.89-3.95 (1H, m, H-5), 3.95-4.10 (2H, m, H-3, H-4), 4.47 (1H, app. s, H-2), 4.68 (1H, d, $J_{1,2}$ 1.8 Hz, H-1).

Example 16

N,N-Dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-glucofuranosyl)sulfinamide (15) ($R_1 = R_2 = C_8H_{17}$):

A solution of *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-glucofuranosyl)sulfenamide (6) in CH_2Cl_2, will be added dropwise to a stirred and cooled solution of *N*-chlorosuccinimide in CH_2Cl_2. Stirring will be continued for 15-30 minutes. After this time sat. aq. $KHCO_3$ will be added with stirring. The organic layer will be separated and dried (K_2CO_3), filtered, and the solvent removed under reduced pressure. The residue will be chromatographed to yield *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-glucofuranosyl)sulfinamide (15).

Example 17

N,N-Dioctyl-*S*-(β-D-glucofuranosyl)sulfinamide (16) ($R_1 = R_2 = C_8H_{17}$):

To a solution of *N,N*-dioctyl-*S*-(2,3,5,6-tetra-*O*-acetyl-β-D-glucofuranosyl)sulfinamide (15) in dry MeOH will be added one equivalent of NaOMe (1M solution in dry MeOH). The reaction will be stirred at room temperature for 2 h under N_2. After this time the solution is to be neutralised with Amberlite IR 120 (H^+) resin, filtered, and the solvent removed under reduced pressure. The residue will be chromatographed to yield *N,N*-dioctyl-*S*-(β-D-glucofuranosyl)sulfinamide (16).

Biological Data

Example 18

Inhibition of *Staphylococcus aureus* by compounds (5) and (8) where $R^1 = R^2 = C_8H_{17}$ is described in Table 1. The biological data were determined by Minimum Inhibitory Concentration (MIC) Assay. Each compound was added to 4 ml of LB broth at a starting concentration of 256 µg/ml. Serial dilutions were then made, 1 in 2 at each step, ending with 2 µg/ml. 5 µL of a saturated culture was added to each serial dilution which were then incubated at 37 °C with shaking for 18 to 20 hours. The MIC_{80} was then determined as the concentration in which there was 80% or greater reduction in growth as compared to the control.

Table 1

Organism tested	Compound*	MIC_{80}
Staphylococcus aureus	5	32 µg/ml
	8	128 µg/ml

* $R^1 = R^2 = C_8H_{17}$

Example 19

Inhibition of various bacteria by compounds (5) and (8) where $R^1 = R^2 = C_8H_{17}$ is described in Table 2. The biological data were determined by a Zone Inhibition Assay method. Compounds were tested by spotting 100 µg of compound as a solution in methanol onto a sterile filter disc placed on a lawn of bacteria on the surface of an LB agar plate. After incubation at 37 °C overnight, the zone of inhibition was measured using an arbitrary scale: +++ = relatively large zone of inhibition, - = no zone of inhibition.

Table 2

Organism tested	Compound*	Zone of inhibition
Staphylococcus aureus	5	++
	8	+
Streptococcus pyogenes	5	+++
	8	+++
Bacillus subtilis	5	+++
	8	+++
Enterococcus faecalis	5	++
	8	++

* $R^1 = R^2 = C_8H_{17}$

Industrial Applicability

The compounds of general formula (I) are useful as pharmaceutical agents, particularly anti-microbial agents.

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